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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/903,109	06/25/92	SCHLEGEL	010091-001

CAPUTA, A

EXAMINER

ART UNIT	PAPER NUMBER
1813	09/23/93

DATE MAILED:

18N1/0922

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-26 and 41-~~46~~ 49 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 27-40 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims _____ are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Part III DETAILED ACTION

1. Applicant's amendment received 6/10/93 has been entered. Claims 27-40 have been canceled. Claims 1-26, and 41-49 are pending.

2. The text of the 35 U.S.C. Code not included in this Office Action can be found in the prior Office Action.

3. The prior rejection of Claims 1-26 and 41-45 (and newly entered claims 46-49) 35 U.S.C. § 112, second paragraph (a) and (e) is withdrawn in view of the applicant's amendment.

The prior rejection of Claims 1-26 and 41-45 (and newly entered claims 46-49) 35 U.S.C. § 112, second paragraph (b),(c) and (d) are withdrawn in view of the applicant's arguments.

4. The prior rejection of claims 15-18, and 20-26 are rejected under 35 U.S.C. § 101 is maintained.

The Examiner's position is set forth in the previous Office Action.

The applicants argues that the recombinantly expressed L1 protein can prevent PV infection in humans since 1.) intact BPV-1 were effective in reducing cysts whereas denatured ones were not in reducing cysts in a xenograft assay, 2.) L1 when produced when

expressed in cos cells unlike bacteria reacted with 4 antibodies that recognize conformational epitopes, 3.) the literature establishes that the in vitro assays predict the ability of papillomavirus proteins to induce neutralization, 4.) a canine model is relevant to human papillomavirus vaccine design since the PV of humans and canine are very similar in structure, 5.) the canine model shows that conformational correct proteins induce protection against PV infection and 6.) Kirnbauer et al. teaches conformationally correct L1 proteins produce a much higher antibody titer than conformationally incorrect L1 proteins.

It is the Examiner's position that there remains to be insufficient evidence that the conformationally correct L1 protein can prevent papillomavirus (PV) infection in humans.

Claims 15-18, and 20-26 are drawn to a L1 protein of HPV for the prevention of papillomavirus infection in humans. The specification provides evidence that human sera and MAb's reactive with intact BPV-1 particles or linear epitopes did not result in cyst reduction (see page 28, lines 20 and 21). In view of the disclosure it is unclear if the murine xenograft assay is useful as a model to predict the use of the conformational L1 protein as a vaccine. The specification further provides evidence that sera from humans did not prevent the infection of BPV-1 on C127 cells. It appears that the in vitro system (infection on C127 cells) is not sufficient to determine the

effectiveness of the claimed protein in view that 1. human sera did not protect PV infection on murine c127 cells 2. it is not clear if the epitopes which are protective are present 3. it is not clear that with active immunization the protective epitopes are maintained to elicit a protective immune response and 4. it is not clear that the antibody response to protective epitopes is high enough to provide protection in vivo. Support of the Examiner's position is provided by the disclosure of the grant application by R. Schlegel, an inventor in the instant application which teaches that experimental models which require artificial means of infection do not permit the best evaluation of a vaccine (see page 28), and assays that utilize rabbit or bovine papillomavirus do not appear to closely mimic the human process (see page 29). In view of the applicant disclosure in the grant proposal provided it would have been expected to an artisan in the art that the use of a bovine papillomavirus is inadequate to determine the efficacy as disclosed in the application in view that it does not closely mimic the human disease process and secondly it requires artificial means of infection. With regards to the applicants arguments that the canine model shows that conformational correct proteins induce protection against PV infection and that Kirnbauer et al. teaches conformationally correct L1 proteins produce a much higher antibody titer than conformationally incorrect L1 proteins it is the Examiner's position that this is insufficient evidence to the

the utility of the protein in view that as admitted by applicant there is no evidence that the L1 by itself is protective. Further it is the Examiner's position that evidence of the L1 in beagles is insufficient evidence that HPV is protective in humans in view that there is no evidence that the protective epitopes or epitopes of HPV and the CPV are shared.

5. The rejection of claims 1-26 and 41-45 under 35 U.S.C. § 112, first paragraph (d) is withdrawn in view of the applicant's arguments.

6. The prior rejection of claims 1-26 and 41-45 (and newly entered claims 46-49) (a), (b), (c), (e) are rejected under 35 U.S.C. § 112, first paragraph is maintained.

a. With regards to claims 15-18, and 20-26 the specification is not enabled for the use of the claimed invention because the utility of the invention has not been proven for the same reasons outlined in the rejection under 35 U.S.C. § 101.

b and e. The specification provides insufficient evidence that hosts such as cattle can elicit an antibody response recognizing conformational epitopes that provide a higher protection than antibodies recognizing linear epitopes. The specification provides evidence that monoclonal antibodies and sera of humans and vaccinated calves which recognize conformational epitopes (see Table 1) don't have a significant different mean size of cyst in comparison to the negative control (see page 28 and Table 2). It appears that polyclonal antibodies from sera of rabbits which recognize conformational epitopes is the only group which has a significantly different mean size of a cyst than the negative control (i.e. normal sera from rabbits). There is insufficient evidence that vaccinated calves or humans

recognize conformational epitopes of BPV-1 or other PV'S to an extent that it provides protection to PV.

The applicants' argue that in view of the high neutralization titers found in the sera and of the significant reduction in the cyst size using steer antisera there is substantial evidence that conformational epitopes of BPV-1 provides substantial protection against BPV-1.

It is the Examiner's position that in view of the disclosure of Table 2 where it is disclosed that the antisera to steer do not have a mean significant size different than the normal sera from rabbits there is insufficient evidence that the vaccinated calves or humans to an extent than it provides a higher protection than normal rabbit serum. In view of the in vivo data it is clear that an artisan would not use in vitro data to determine the efficacy of a vaccine.

The specification further teaches that not only is the L1 expressed recombinantly in cos, useful for a vaccine but also for serological detection and typing (see page 48). The specification provides no evidence that a L1 expressed recombinantly is type specific for PV.

The applicant argues that the HPV-1 expressed in cos cells has been shown to bind 4 antibodies specific to HPV-1 virus.

It is the Examiner's position that in view that is not clear as to were in the specification it is disclosed that the L1 of the HPV-1 is specifically recognized by 4 monoclonal antibodies that are serotype specific and since there is no guidance that antibodies to the L1 are specific the rejection is maintained.

The specification provides insufficient guidance that the recombinant L1 and portions thereof are capable of reproducing the antigenicity or substantially of all proteins found of the intact papillomavirus. For instance the specification provides insufficient guidance that the L1 is substantially antigenic as the intact PV in a vaccine and/or diagnosis.

The applicant's argue that in view that the recombinant L1 mimics the native L1 it substantially reproduces the antigenicity of the intact papillomavirus. It is the Examiner's position that in view that there are other proteins which are antigenic in PV the specification provides insufficient evidence that the antigenicity of L1 is substantially equivalent to all the proteins of the intact PV the rejection is maintained.

c. The applicant argues that given the information the information in this application one could identify those portions capable of binding to conformation specific epitopes.

It is the Examiner's position that the specification provides insufficient guidance as to which portions of the claimed are useful for the protection of PV and are capable of reproducing the antigenicity of the intact virus. It would be expected that portions of the protein which are hydrophobic would be poorly immunogenic and not useful for the detection and/or protection of PV. Prior art at the time of the invention predicts with no certainty that a portion is antigenic. Stern teaches of the problems of predicting antigenic sites on

proteins. Stern teaches that one problem of predicting antigenic sites is whether all antigenic sites on the protein in question have been found (see page 166, Column 2 and 3) and that the sequence alone is not necessarily a determinant of immunogenicity (see page 167). Berzofsky teaches that although intrinsic factors (i.e. hydrophilicity and mobility) may determine the repertoire of potential antigenic sites, only a subset of these sites will elicit antibodies (see page 937, Column 1 and 2). It would be expected therefore that the prior art teaches of potential peptides which may be antigenic sites however the identity of those peptides which are antigenic can only be determined with immunization studies. It is the Examiner's position that given that those peptides which are immunogenic can only be determined with immunization studies it would be undue experimentation to determine which portions are antigenic.

7. The prior rejection of claims 1, 10, 12-14, 18-21, and 25 directed to the antigenic portions of the L1 protein under 35 U.S.C. § 102(b) as being anticipated by Danos et al is maintained.

Danos et al. disclose of using peptides of HPV 1 type (e.g. 1a) contained in the L1 region for a vaccine. Danos et al. disclose that the fragment can expressed by a suitable microorganism (see Column 3). Danos et al discloses (see Column 6) that the peptide can be coupled to a carrier such as serum albumins preferably animal when it relates to vaccines intended for veterinary use. It is anticipated that this includes BSA. Danos et al. discloses (see Column 6) that the peptide can be useful or a vaccine in humans.

The applicant argues that in view that Danos et al. teaches of linear epitopes in contrast to the application which discloses of conformationally correct L1 proteins which substantially reproduces the antigenicity of PV virions the rejection should be withdrawn.

It is the Examiner's position in view that the claimed invention is drawn to antigenic fragments which encompasses the peptides of the prior art and substantially reproducing the antigenicity of the intact papillomavirus can be interpreted as effective as vaccine the claimed subject matter is anticipated over the prior art.

8. The prior rejection of claims 1-26 and 41-45 (and newly amended claims 46-49) under 35 U.S.C. § 103 as being unpatentable over Christensen et al., Pilacinski et al., Sambrook et al. and Danos et al. is maintained.

Pilacinski et al. teaches that fused proteins of L1 and L2 BPV-1 cloned and expressed in E. coli. Pilacinski et al. teaches that although the antisera generated against the fusion proteins react specifically with BPV-1 to be useful as a vaccine the proteins must elicit an immunological immune response that prevents infection (see page 359, lines 1-5). Pilacinski et al. further teaches (see page 359, Column 2) that a majority of the BPV-1 specific antigenic sites were not presented to the immune system in animals and this could be due to non-natural conformation of the BPV portion. Pilacinski et al. teaches (see page 360, last paragraph) that Beta-gal fusion proteins often are insoluble forming aggregates. Pilacinski et al. does not teach of expressing the L1 protein using mammalian cells to provide a L1 protein which is protective.

Christensen et al. (1990) teaches of neutralizing epitopes of HPV-11 infectious particles by monoclonal antibodies.

Christensen et al. teaches the epitope(s) represent external nonlinear determinants.

It would have been obvious to one of ordinary skill in the art at the time of the invention that specific antigenic sites of L1 and L2 not presented to the immune system in animals are due to the non-natural conformation of the BPV (see Pilacinski et al.) specifically the lack of conformational epitopes, since conformational epitopes were identified as neutralizing epitopes as described by Christensen et al.

Sambrook et al. teaches (see page 16.3) that one problem of expressing proteins in bacteria are that they are folded incorrectly and consequently exhibit low specific activities. Sambrook et al. teaches a solution is the expression of proteins in mammalian cells such as SV40 and baculoviruses. Sambrook et al. teaches of several plasmid SV vectors that can be used to express the protein of interest in cos cells. It would have been obvious to one of ordinary skill in the art at the time of the invention to express the L1 protein using the method described by Sambrook et al. since it would have been expected that with the use of baculoviruses and SV40 plasmid vectors known in the art at the time of the invention would fold correctly. It would have been expected that the recombinant L1 of other PV's and other selected types of HPV would protect against the respective PV.

Danos et al. teaches (see Column 6) that the peptide can be coupled to a carrier such as serum albumins preferably animal when it relates to vaccines intended for veterinary use. It would have been obvious to couple antigenic portions of HPV using serum albumins to as described by Danos et al. to enhance immunogenicity.

Applicants' argue that it was not expected that the L1 would be folded correctly when expressed in mammalian cells and substantially reproduce the antigenicity of the intact PV virion. This is not persuasive in view that Sambrook et al. teaches (see page 16.3) that one solution of expressing proteins in bacteria which are folded incorrectly and consequently exhibit low specific activities, is the expression of proteins in mammalian cells such as SV40 and baculoviruses.

Applicant's argue that SV40 would not have suggested the efficacy of the present invention given differences in the SV40

and the PV. This is not persuasive since the SV 40 system is described to be an expression system for the expression of a variety of proteins as described by Sambrook et al.

Applicant argue that the L2 protein might have been necessary for the antigenicity of L1 and the applicant's invention is the first to provide evidence that L1 by itself may provide protection. This is not persuasive in view that claimed subject matter is drawn to a recombinant L1 protein which is capable of substantially reproducing the antigenicity of the intact virions, the recombinant L1 protein as claimed encompasses a fusion protein of L1 and l2, the vaccine claims do not exclude the L2, and finally the teachings of Danos and/or Pilacinski et al. Danos discloses that peptides of L1 are protective and Pilacinski et al. teaches that proteins useful as a vaccine must elicit an immune response, such as L1 which produces a stronger and more consistent response than L2 (see page 359, Column 1, last paragraph).

Finally the applicant argues that the results are unexpected in view that recombinant protein produced in insect cells is 1000 fold higher than in E.coli. This is not persuasive since the epitopes which are protective appear to be conformational, and making the protein in a eucaryotic host as disclosed by Sambrook would have been expected to one of ordinary skill in the art to provide a significantly higher neutralizing titer.

Thus the claimed invention as a whole is clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ghim et al. teaches (see abstract) of polyclonal and monoclonal antibodies to react specifically with conformational epitopes of the HPV-1 L1 protein. Ghim et al. teaches that the screening of capsid protein of PV for reactivity with conformation dependent antibodies represents a method to ensure that such proteins will be suitable for vaccine development or detection of human PV infections.

New Grounds of Rejection

9. Claims 1-26 and 41-49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-26 and 41-49 are vague and indefinite in view that the claimed recombinant protein or fragment capable of substantially reproducing the antigenicity of intact papillomavirus can be interpreted as a protein or fragment that has 1, 5, 10, or 50 epitopes.

10. The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification as filed does not support provide support the invention as now claimed.

The amended claims recite an antigen or antigenic fragment which is capable of substantially reproducing the antigenicity of the intact PV. The specification as originally filed provides support for an antigen or antigenic fragment which is capable of reproducing the antigenicity of the intact PV and not of an antigen or fragment substantially reproducing the antigenicity as disclosed in the original claims and instant application (see page 4, lines 4 and 5).

11. Claims 1-26 and 41-49 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

12. The amendment received 6/10/93 (Paper No. 8) is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: ... protein is capable of substantially reproducing the antigenicity of the intact papillomavirus virions.

Applicant is required to cancel the new matter in the response to this Office action.

13. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

14. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0916.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4227.

Anthony C. Caputa, Ph.D.

September 19, 1993

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